Title: A re-examination of the Beta-blocker Evaluation of Survival Trial (BEST) using composite outcomes including emergency department visits

Short title: A re-examination of BEST

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ABSTRACT

Objectives: We examined the influence of choice of endpoint on trial size, duration and interpretation of results in patients with heart failure enrolled in the Beta-blocker Evaluation of Survival Trial (BEST).

Background: The choice of endpoints in heart failure trials has evolved over the last decades.

Methods: In the BEST trial we examined the effect of bucindolol on the now standard composite of cardiovascular death or heart failure hospitalization (CVD/HFH), compared with the original primary mortality endpoint, and the expanded composite including emergency department (ED) visits using Cox regression analysis. We also undertook an analysis of recurrent events primarily using Lin, Wei, Ying and Yang model.

Results: Overall, 448 (33%) placebo patients and 411 (30%) bucindolol patients died (HR 0.90; 95% CI 0.78-1.02; p=0.11). 730 (54%) patients experienced CVD/HFH on placebo and 624 (46%) on bucindolol (0.80; 0.72-0.89; p<0.001). Adding ED visits increased these numbers to 768 (57%) and 668 (49%), respectively (0.81; 0.73-0.90; p<0.001). 568 (42%) placebo patients experienced HFH compared with 476 (35%) bucindolol patients (0.78; 0.69-0.89; p <0.001) with a total of 1333 and 1124 admissions, respectively. With the same statistical assumptions, using the composite endpoint instead of all-cause mortality would have reduced the trial size by 40% and follow-up duration by 69%. The rate ratio for recurrent events (CVD/HFH) was 0.83 (0.73-0.94), p=0.003.

Conclusion: Choice of endpoint has major implications for trial size and duration, as well as interpretation of results. The value of broader composite endpoints and inclusion of recurrent events needs further investigation.

Keywords: heart failure, BEST, endpoint, recurrent events

Abbreviations and acronyms:

BEST = Beta-blocker Evaluation of Survival Trial

CI =confidence interval

CV =cardiovascular

ED =emergency department

HF =heart failure

HR =hazard ratio

LVEF=left ventricular ejection fraction

NYHA =New York Heart Association

WLW =Wei, Lin and Weissfeld

LWYY =Lin, Wei, Ying and Yang

INTRODUCTION

The choice of endpoints in heart failure (HF) trials has evolved over the past three decades. Initially, death from any cause was commonly used as the primary endpoint but with incremental improvements in therapy it has become more common to use mortality-morbidity composite outcomes (1-3). In part, these reflect improving survival in HF and the resultant feasibility and affordability of conducting mortality trials. However, incorporation of hospital admissions for HF in composites also recognizes the importance of these non-fatal events to the overall burden of HF and their economic significance (4-6). More recently, cardiovascular (CV) rather than all-cause mortality has been incorporated in composite outcomes. This recognizes the likely absence of effect of novel treatments for HF on non-cardiovascular death and the growing proportion of deaths attributable to non-cardiovascular causes because of the cumulative benefits of effective treatments on cardiovascular mortality (7-9). Similarly, with improving survival and chronicity of HF, it has been suggested that analysis of all events, including repeat events, better reflects the overall burden of the condition than the conventional time-to-first event analysis (10-14). Most recently, clinical practice has evolved, particularly in the United States, to attempt to manage episodes of HF worsening without formal admission to hospital. This potentially means that HF hospitalization may no longer reflect the true extent of treatment failure. Consequently, it has been suggested that these non-hospitalized episodes should be included in composite outcomes (5,15,16). However, there are few data on the frequency of occurrence of these and whether or not they respond to study treatment in the same way as hospital admission.

We used the Beta-blocker Evaluation of Survival Trial (BEST) to examine the implications of this evolution in trial endpoints in heart failure with reduced ejection fraction (HF-REF) (17,18). BEST is of particular interest because information of emergency department (ED) visits, as well as HF hospitalizations, was collected systematically during the trial.

METHODS

Study design and patients

BEST was a randomized double-blind trial of bucindolol in patients with HF, funded by the National Heart, Lung, and Blood Institute (NHLBI) and the Department of Veterans Affairs (17,18). The BEST protocol and results have been published. In brief, 2708 HF patients with a left ventricular ejection fraction (LVEF) ≤35% and New York Heart Association (NYHA) class III or IV symptoms were enrolled in the United States and Canada from 1995 to 1998 and randomly assigned to receive bucindolol or placebo. The primary endpoint was death from any cause. The secondary endpoints included CV death and HF hospitalization. The cause of death was adjudicated blindly by the central endpoint committee. The de-identified public-use copy of the BEST database provided by the NHLBI, which included all but one participant, was used for the current analysis.

Outcomes

HF hospitalizations and ED visits for HF were reported by investigators. Specifically, the investigator was asked on the hospitalization or ED visit form to state whether the visit was due to worsening HF ("yes" or "no"), where investigators were instructed to select "yes" only if the visit was due to decompensated HF. We defined an isolated ED visit for HF as one which occurred without a subsequent HF hospitalization within 30 days, and if patients were hospitalized within 30 days after an ED visit, they were classified as having a HF hospitalization. The outcomes of interest in this analysis included: the composite of time to first HF hospitalization or CV death; the expanded composite of time to first CV death, HF hospitalization or ED visit for HF; all HF hospitalizations (including repeats); and a composite of all HF hospitalizations and CV death (each CV death was counted as an additional event except when a patient died during a HF admission).

Statistical analyses

Time to first event analyses

The baseline characteristics of patients having first isolated ED visit for HF, HF hospitalization or CV death or none of these events were compared using ANOVA for continuous variables and Chi-square test for categorical variables. HF duration was not normally distributed and thus was compared using Kruskal-Wallis test.

The association between a first non-fatal event (ED visit for HF or HF hospitalization) and subsequent mortality was examined using time-updated Cox regression analysis with patients with neither event as the reference group. The association was adjusted for treatment assignment and baseline covariates including age, sex, race, systolic blood pressure, heart rate, BMI, LVEF, NYHA class, ischemic etiology, hypertension, diabetes, myocardial infarction, atrial fibrillation, previous implantable cardioverter defibrillator and serum creatinine. Treatment effect on the composite, and on the expanded composite and its components was examined using Cox regression analysis.

Assuming all-cause mortality, the composite or the expanded composite as the endpoint, we examined the time taken to accrue a certain number of the assumed events, and also examined the sample size required to detect 20% reduction in the assumed endpoint with bucindolol therapy using log-rank test assuming a two-sided significant level of 5%, statistical power of 85%, equal allocation, 3-year uniform accrual period, a minimum follow-up of 1 year and a maximum follow-up of 4 years.

Recurrent events analysis

Recurrent events are commonly analyzed using count data methods, e.g. negative binomial regression, and using time-to-event data methods, e.g. Andersen-Gill, Wei, Lin and Weissfeld (WLW), and Lin, Wei, Ying and Yang (LWYY) models, all of which are extensions of Cox proportional hazards regression (10-13). There is debate about which of these approaches is best to use and some considerations around this debate are outlined in the Supplement. As in the present study, the event rate and treatment effect were

not constant during follow-up, which violate the assumption of negative binomial regression; therefore, the LWYY model was used as the primary method and the negative binomial and WLW regressions as sensitivity analyses.

We calculated the HF hospitalization rate by treatment group by dividing the total number of HF hospitalizations by the total number of follow-up years in each group. The cumulative rates of HF hospitalizations over time by treatment group were plotted using the non-parametric Ghosh and Lin method, accounting for the competing risk of death. Treatment effect on all HF hospitalizations and on the composite of all HF hospitalizations and CV death was analyzed primarily using the LWYY model, and additionally using the negative binomial and WLW regressions. Given the inconstant treatment effect on HF hospitalization over time, sensitivity analyses were performed by assessing the treatment effects within 6 months and beyond 6 months since randomization. To account for the association between HF hospitalization and subsequent mortality and the competing risk of mortality on HF hospitalizations, the joint frailty model was used to analyze recurrent HF hospitalizations and time to CV death simultaneously.

A two-sided p value <0.05 was considered significant. The recurrent event analysis was undertaken using R (version 3.2.3). All other analyses were performed using the Stata version 14 (College Station, TX, USA).

RESULTS

Of the 2707 patients analyzed, 1353 were randomized to placebo and 1354 to bucindolol. The median duration of follow-up was 2.0 years.

Deaths: Overall, 448 patients (33%) assigned to placebo and 411 (30%) assigned to bucindolol died with a hazard ratio (HR) in the bucindolol group of 0.90 (95% CI: 0.78 to 1.02; p=0.11). The number in each treatment group who died from a CV cause was 388 (29%) and 342 (25%) respectively (HR, 0.86; 95% CI: 0.75 to 1.00; p=0.045).

Hospital admissions for HF: Overall, 568 patients (42%) assigned to placebo and 476 (35%) assigned to bucindolol had a HF hospitalization (HR 0.78; 95% CI, 0.69 to 0.89; p <0.001). There was a total of 1333 admissions in the placebo group and 1124 in the bucindolol group (Table 1).

ED visits for HF: A total of 334 placebo treated patients (25%) had an ED visit for HF; this number was 281 (21%) in the bucindolol group, HR 0.81 (95% CI 0.69 to 0.95), p=0.01. Of these, 161 (11.9% of all patients) and 138 (10.2%) patients, respectively, were not admitted to hospital (48% and 49% of patients, respectively, presenting to the ED were not admitted), HR 0.84 (95% CI 0.67 to 1.06), p =0.14. Overall, there were 586 ED visits for HF in the placebo group and 510 in the bucindolol group. Of these, 211 (36% of visits) and 176 (35%) respectively did not result in a proximate hospital admission (Table 1).

Characteristics of patients with an adverse outcome: The baseline characteristics of patients experiencing a CV death, HF hospitalization or ED visit for HF (or none of these) are shown in Table 2. Overall patients who died had more characteristics associated with worse outcome (e.g. older age, lower blood pressure, estimated glomerular filtration rate and LVEF, ischemic etiology, NYHA class IV) and those who had no event had the least of these characteristics. Patients with HF

hospitalization and ED visits were in-between these two extremes, although patients with ED visits appeared less sick, overall, compared with those hospitalized.

Association between HF worsening and subsequent mortality: Compared to patients not experiencing an ED visit (or HF hospitalization), those with an ED visit for HF were subsequently twice as likely to die during follow-up (HR, 2.05; 95% CI: 1.47 to 2.84; p <0.001), even after adjustment for other prognostic variables, HR 1.90 (1.37 to 2.65), p <0.001. In similar analyses, patients hospitalized for worsening HF were four times as likely to die; unadjusted HR 4.65 (4.02 to 5.37), adjusted HR 3.72 (3.20 to 4.33), both p <0.001.

Composite clinical outcomes: The number of patients experiencing the composite of first HF hospitalization or CV death was 730 (54%) and 624 (46%) in the placebo and bucindolol groups, respectively; HR 0.80 (95% CI 0.72 to 0.89), p <0.001. Adding ED visits for HF increased the numbers of patients affected to 768 (57%) and 668 (49%), respectively; HR 0.81 (0.73 to 0.90), p<0.001 (Figure 1).

Implications for trial size and duration: The number of days taken to accrue 500 patients with a death from any cause was 515, for the composite of HF hospitalization or CV death this figure was 162 days and for the expanded composite including ED visits it was 136 days. There was a substantial decrease in the sample size when using the composite outcomes. For example, with a power of 85% to detect 20% reduction in the bucindolol group at a significant level of 5%, the sample size was 2454 for death from any cause, 1524 for the composite and 1432 for the composite including ED visits.

Recurrent HF hospitalizations: There were a total of 1333 HF hospitalizations in the placebo group and 1124 in the bucindolol group, including 765 (57.4% of all admissions) and 648 (57.7%) repeated admissions, respectively. The frequencies of HF hospitalizations by treatment group were presented in Table 1. Over 25% of all HF admissions occurred within 6 months of randomization, and the figure was 25.2% (n=336) in the placebo group and 29.3% (n=329) in the bucindolol group (Supplement Figure A).

The HF hospitalization rates were 49.5 and 40.8 per 100 patient-years in the placebo and bucindolol groups, respectively. Compared to the placebo group, the cumulative rate in the bucindolol group was lower after 6 months, although before 6 months it was slightly higher, i.e. the cumulative event curves "crossed-over" at about 6 months. The corresponding cumulative rate ratio (bucindolol vs. placebo) appeared to remain constant at approximately 0.83 after 6 months (Figure 2).

Patients having at least one HF hospitalization were more likely to have baseline characteristics associated with worse outcomes (Supplement Table A).

For all HF hospitalizations, the LWYY regression model gave an overall HR for bucindolol of 0.82 (95% CI 0.71 to 0.95, p=0.008). A similar estimate was observed from the WLW model (0.80, 0.68 to 0.94, p=0.005), while a smaller and non-significant effect was obtained from negative binomial and joint frailty models (both gave a rate ratio of 0.89, with 95% CI 0.77 to 1.04) (Table 3). However, when separate estimations were made for the first 6 months and the remainder of follow-up, the results were consistent across different methods. Based on the LWYY model, the estimate was 0.98 (95% CI 0.80 to 1.21, p=0.88) within 6 months and 0.77 (0.65 to 0.91, p=0.002) after 6 months. Nearly identical estimates were observed for the composite of all HF hospitalizations and CV death from the corresponding regression models (Table 3).

DISCUSSION

The purpose of this study was to illustrate the implications of the choice of primary endpoint in clinical trials in HF-REF and how this choice has evolved (and continues to evolve) in recent years. Perhaps the most striking conclusion is that, had the primary endpoint most commonly used in recent HF trials been used in BEST, the trial would have clearly been "positive" instead of "neutral" or "negative" as it is historically regarded. This difference reflects two things. Firstly, the much larger number of events in the composite outcome (1354 versus 859 deaths) and the fact that 129 deaths were non-cardiovascular. While a larger number of events, *per se*, does not increase statistical power, HF hospitalizations are events likely to be favourably influenced by an effective therapy and therefore did increase power. Conversely, a beta-blocker was unlikely to decrease the risk of non-cardiovascular death meaning that the 15% of deaths that were not cardiovascular effectively diluted the benefit of bucindolol on the original primary endpoint (by adding "noise"). As a result, switching from an all-cause mortality endpoint to the composite of CV death or HF hospitalization would have had a dramatic impact on sample size in BEST – assuming the same treatment effect-size, power and significance level (20%, 85% and 5%, respectively), the sample size would have been reduced by nearly 40% (from n=2454 to 1524) and the time taken to accrue a requisite number of endpoints (e.g. n=500) reduced by an even greater amount (515 to 162 days, a 69% reduction).

While we found bucindolol reduced the composite of CV death or HF hospitalization, a broader composite including ED visits, and recurrent events, it did not reduce all-cause mortality, as demonstrated with three other beta-blockers (19). The reason for this remains uncertain although the specific pharmacologic properties of bucindolol, the racial mix of the population studied in BEST and interactions between the two have been implicated (20,21).

Despite a benefit of bucindolol on the composite of CV death or HF hospitalization, an early increase in HF hospitalization was observed among patients treated with bucindolol. HF worsening is a recognized risk early after initiation of beta-blocker treatment and is thought to be minimized by starting with a low-dose of treatment. This finding was also seen in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) although apparently not in the Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS) which also enrolled patients with more severe HF, as in BEST (the relevant analysis has not been reported for the second Cardiac Insufficiency Bisoprolol Study, CIBIS-2) (22-24). However, the dose up-titration rate in BEST was more rapid (weekly) than in the other trials (two-weekly in COPERNICUS and MERIT-HF; weekly to 5mg in CIBIS-2 and then four-weekly). Another possible reason could be the potent sympatholytic effect of bucindolol. Another analysis of BEST showed that a decrease in plasma norepinephrine levels after 3 months of treatment was associated with higher risk of death or HF hospitalization in the bucindolol group (25).

Because of changing practice, it has been suggested that composite outcomes be further expanded to include episodes of HF worsening that do not lead to formal hospital admission (5,15,16,26,27). BEST was unusual in systematically documenting ED visits. Although not as numerous as HF hospitalizations, ED visits were common. However, most were associated with a hospital admission shortly thereafter. Consequently, in a time to first event analysis, isolated ED visits added relatively few unique events (5%). Nevertheless, these were enough to shorten the time to accrual of a target number of events (as used in an event-driven trial) by around 15%. There may be concerns about inclusion of ED visits in the composite outcome (5,15,16,26,27). Firstly, these events may not reflect worsening of HF in the same way as hospitalization either because the events may be less severe or because patient evaluation during an ED visit may be less comprehensive than during a hospital admission and diagnosis less certain. For these reasons, ED visits may also be less responsive to the experimental treatment (especially if there is mis-diagnosis). Nevertheless,

scrutiny of the characteristic of patients with ED visits showed they had features associated with worse outcomes, although less advanced than in patients who were hospitalized or died. In keeping with this, patients with an ED visit in BEST were subsequently twice as likely to die compared to those without an ED visit (or hospitalization for HF), confirming the findings of another more recent trial and some epidemiological data (16,27); patients hospitalized with worsening HF were four times as likely to die. The effect of bucindolol on ED visits was similar to that on CV death and on HF hospitalization. Consequently, including ED visits in the composite outcome would not only have reduced the study size (from 1524 to 1432 in the scenario outlined above) and shortened the time to accrual of a target number of events (e.g. from 162 to 132 days for 500 events) but would also have slightly narrowed the 95% CIs around the point estimate for the effect of bucindolol.

As survival has increased, HF has become a more chronic condition with recurrent non-fatal hospitalizations an increasingly important reflection of the overall burden of the disease on patients and health care systems alike. This has led to the suggestion that analysis of all events, including repeat hospital admissions, may provide a better evaluation of the effect of treatment than time-to-first event analysis which has been the conventional approach used to estimate treatment-effect in clinical trials (5,11-15). A variety of statistical approaches can be employed to do such analyses and there has been discussion about which of these is best to use. We found the two most commonly advocated approaches (i.e. negative binomial and joint frailty models) showed somewhat less favourable treatment effects than the WLW model and LWYY model (the principal method in this study). This may result from the violation of two important assumptions of negative binomial regression in BEST, i.e. the constant event rate and the constant treatment effect over time. This was also the case for the joint frailty model which is in effect a combination of negative binomial regression for recurrent HF hospitalizations and Cox regression for time to CV death. The rate of HF hospitalizations was relatively high early after randomization (i.e. over the first 6 months) and

lower thereafter. As mentioned above, bucindolol treatment led to an early increase in risk of HF hospitalization followed by a later decrease. When estimations were made separately within 6 months and beyond 6 months, fairly consistent results were observed using the different modelling approaches.

Interestingly, the proportional reduction in risk estimated using all of these methods was smaller than obtained in conventional time-to-first event analysis. The reason for this observation is uncertain but may reflect the early increase in hospitalization following initiation of bucindolol before the longer-term reduction in recurrent events with this treatment became evident. If correct, and whatever the reason, these findings highlight the need to better understand the effect of therapies on recurrent events and how analyses of these might be used in future clinical trials.

As with all studies, there are limitations. Firstly, this was a *post hoc* analysis. Secondly, it has been argued that the actions of bucindolol may be unique among the beta-blockers tested in large outcome trials although the benefits observed in BEST were generally in keeping with those seen in the other trials (20,28). Thirdly, there was potential violation of proportional hazards assumption for the Cox models in the composite and the expanded composite outcome analyses, given the cross-over in the Kaplan-Meier curves, although the Schoenfeld residuals test was not significant for either (both p value >0.05). Lastly, we only used investigator reported HF hospitalizations and ED visits in our analyses; however, a previous analysis showed a similar treatment effect of bucindolol on first hospitalizations for HF when adjudicated events were used instead (29).

In summary, choice of endpoint has major implications for trial size and duration, as well as interpretation of results. The use of broader composite endpoints that include non-hospitalized manifestations of HF worsening may further reduce sample size and trial length. However, the role of additional manifestations of worsening other than ED visits needs further study. Similarly, the

potential role of analysis of recurrent events as a trial endpoint needs further investigation. This type of analysis may not give the same estimate of treatment effect as time-to-first event analysis, although the level of agreement may differ for different treatment. This finding does, however, raise the interesting question as to which approach, time-to-first event analysis or analysis of all (first and recurrent) events, gives the more clinically relevant answer?

Clinical Perspectives

The choice of primary endpoints has major influence on trial size and duration and on the interpretation of results. The use of broader composite endpoints including ED visits for HF worsening may further reduce trial size and length.

Translational Outlook

Further studies are required to determine the values of broader composite endpoints and inclusion of recurrent events, and to standardize the approach for the analysis of recurrent events if included as endpoints.

REFERENCES

1. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987;316:1429-35.
2. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:293-302.
3. Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.
4. Neaton JD, Gray G, Zuckerman BD, Konstam MA. Key issues in end point selection for heart failure trials: composite end points. J Card Fail 2005;11:567-75.
5. Anker SD, Schroeder S, Atar D et al. Traditional and new composite endpoints in heart failure clinical trials: facilitating comprehensive efficacy assessments and improving trial efficiency. Eur J Heart Fail 2016;18:482-9.
6. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. Eur J Heart Fail 2002;4:361-71.
7. Rush CJ, Campbell RT, Jhund PS et al. Falling Cardiovascular Mortality in Heart Failure With Reduced Ejection Fraction and Implications for Clinical Trials. JACC Heart Fail 2015;3:603-14.
8. Jhund PS, Macintyre K, Simpson CR et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation 2009;119:515-23.
9. Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden; Data from the Swedish Hospital Discharge Registry 1988 to 2000. Eur Heart J 2004;25:300-7.
10. Rogers JK, Jhund PS, Perez AC et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). JACC Heart Fail 2014;2:289-97.
11. Rogers JK, Pocock SJ, McMurray JJ et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. Eur J Heart Fail 2014;16:33-40.
12. Rogers JK, McMurray JJ, Pocock SJ et al. Eplerenone in patients with systolic heart failure and mild symptoms: analysis of repeat hospitalizations. Circulation 2012;126:2317-23.
13. Anker SD, McMurray JJ. Time to move on from 'time-to-first': should all events be included in the analysis of clinical trials? Eur Heart J 2012;33:2764-5.
14. Goldenberg I, Hall WJ, Beck CA et al. Reduction of the risk of recurring heart failure events with cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011;58:729-37.
15. Skali H, Dwyer EM, Goldstein R et al. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. Eur J Heart Fail 2014;16:560-5.
16. Okumura N, Jhund PS, Gong J et al. Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting: Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). Circulation 2016;133:2254-62.
17. Design of the Beta-Blocker Evaluation Survival Trial (BEST). The BEST Steering Committee. Am J Cardiol 1995;75:1220-3.
18. Beta-Blocker Evaluation of Survival Trial I. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344:1659-67.

19. Domanski MJ, Krause-Steinrauf H, Massie BM et al. A comparative analysis of the results from 4 trials of beta-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. J Card Fail 2003;9:354-63.
20. O'Connor CM, Fiuzat M, Carson PE et al. Combinatorial pharmacogenetic interactions of bucindolol and beta1, alpha2C adrenergic receptor polymorphisms. PLoS One 2012;7:e44324.
21. Taylor MR, Sun AY, Davis G, Fiuzat M, Liggett SB, Bristow MR. Race, common genetic variation, and therapeutic response disparities in heart failure. JACC Heart Fail 2014;2:561-72.
22. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.
23. Hjalmarson A, Goldstein S, Fagerberg B et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000;283:1295-302.
24. Packer M, Fowler MB, Roecker EB et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106:2194-9.
25. Bristow MR, Krause-Steinrauf H, Nuzzo R et al. Effect of baseline or changes in adrenergic activity on clinical outcomes in the beta-blocker evaluation of survival trial. Circulation 2004;110:1437-42.
26. Lee DS, Schull MJ, Alter DA et al. Early deaths in patients with heart failure discharged from the emergency department: a population-based analysis. Circ Heart Fail 2010;3:228-35.
27. Ezekowitz JA, Kaul P, Bakal JA, Quan H, McAlister FA. Trends in heart failure care: has the incident diagnosis of heart failure shifted from the hospital to the emergency department and outpatient clinics? Eur J Heart Fail 2011;13:142-7.
28. Liggett SB, Mialet-Perez J, Thaneemit-Chen S et al. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. Proc Natl Acad Sci U S A 2006;103:11288-93.
29. Carson P, Fiuzat M, O'Connor C et al. Determination of hospitalization type by investigator case report form or adjudication committee in a large heart failure clinical trial (beta-Blocker Evaluation of Survival Trial [BEST]). Am Heart J 2010;160:649-54.

FIGURE LEGEND

Figure 1 Kaplan-Meier curves for composite outcome (A) and the expanded composite outcome (B) according to treatment group.

Figure 2 Estimated cumulative rate of heart failure hospitalizations per 100 patients over time by treatment group and the corresponding risk ratio (bucindolol versus placebo) for the cumulative rate of heart failure hospitalizations.

TABLE LEGEND

Table 1 Number of heart failure hospitalizations and emergency department visits for heart failure by treatment group in BEST.

Table 2 Baseline characteristics of patients with first emergency department visit for heart failure, heart failure hospitalization, or neither, or experiencing cardiovascular death.

Table 3 Treatment effects (bucindolol versus placebo) on all heart failure hospitalizations (first and recurrent) and the composite of all heart failure hospitalizations and cardiovascular deaths using different methods to analyse recurrent events.

SUPPLEMENT

Discussion of approaches to analysis of recurrent events.

Supplement Table A Baseline characteristics according to the number of heart failure hospitalizations.

Supplement Figure A Distribution of time from randomization to any heart failure hospitalization by treatment group.

Table 1 Number of heart failure hospitalizations and emergency department visits for heart failure by treatment group in BEST.

	Placebo	**Bucindolol**
Number of patients	1353	1354
Total years of follow-up	2694	2755
Number of deaths	448	411
Number of CV deaths	388	342
HF hospitalization		
Patients with ≥1 hospitalization	568	476
Patients with ≥2 hospitalizations	323	246
Number of HF hospitalizations	1333	1124
Patients with number of hospitalizations		
1	245	230
2	152	97
3	74	61
4	32	27
5	27	24
6	17	13
7	7	9
8	4	4
9	2	4
10	3	3
11	0	1
12	3	1
13	0	1
14	0	1

16	2	0
ED visit for HF		
Patients with ≥1 ED visit	334	281
Patients with ≥2 ED visits	122	97
Number of ED visits	586	510
Isolated ED visit for HF		
Patients with ≥1 isolated ED visit	161	138
Patients with ≥2 isolated ED visits	31	25
Number of isolated ED visits	211	176

CV denotes cardiovascular; ED, emergency department; HF, heart failure.

Table 2 Baseline characteristics of patients with first emergency department visit for heart failure, heart failure hospitalization, or neither, or experiencing cardiovascular death.

	No relevant event	ED visit for HF	HF hospitalization	CV death	p value
n (%)	1271 (47.0)	199 (7.4)	986 (36.4)	251 (9.3)	
Age -year	59.1±12.4	59.6 ±12.2	61.2±12.3	62.8±11.9	<0.001
Male sex -n (%)	982 (77.3)	155 (77.9)	776 (78.7)	201 (80.1)	0.727
Race -n (%)					0.055
White	911 (71.7)	133 (66.8)	662 (67.1)	189 (75.3)	
Black	274 (21.6)	48 (24.1)	256 (26.0)	49 (19.5)	
Hispanic	67 (5.3)	11 (5.5)	56 (5.7)	9 (3.6)	
Other	19 (1.5)	7 (3.5)	12 (1.2)	4 (1.6)	
Blood pressure -mmHg					
Systolic	119.5±17.9	116.7±18.5	114.5±17.8	115.7±17.9	<0.001
Diastolic	72.3±11.2	71.8±11.8	69.9±10.9	68.8±11.1	<0.001
Heart rate -beats/min	81.4±13.0	81.2±13.9	82.1±13.4	81.1±12.8	0.566
BMI - kg/m^2	28.3±6.0	29.1±6.4	27.5±5.7	27.1±5.4	<0.001
HF duration* -months	30 [10-64]	39 [10-72]	41 [16-75]	46 [13-78]	<0.001

Left ventricular ejection fraction -%	24.4±7.0	23.0±7.1	21.7±7.3	21.6±7.1	<0.001
NYHA class -n (%)					<0.001
III	1208 (95.0)	184 (92.5)	869 (88.1)	220 (87.7)	
IV	63 (5.0)	15 (7.5)	117 (11.9)	31 (12.4)	
Ischemic etiology -n (%)	672 (52.9)	111 (55.8)	623 (63.2)	181 (72.1)	<0.001
Medical history -n (%)					
Myocardial infarction	485 (38.2)	75 (37.7)	452 (45.8)	132 (52.6)	<0.001
Angina	618 (48.6)	107 (53.8)	535 (54.3)	140 (55.8)	0.024
CABG	331 (26.0)	60 (30.2)	303 (30.7)	88 (35.1)	0.010
PCI	189 (14.9)	35 (17.6)	161 (16.3)	38 (15.1)	0.672
Hypertension	720 (56.6)	126 (63.3)	598 (60.6)	151 (60.2)	0.129
Diabetes	393 (30.9)	84 (42.2)	380 (38.5)	107 (42.6)	<0.001
Atrial fibrillation	263 (20.7)	39 (19.6)	283 (28.7)	68 (27.1)	<0.001
Treatment -n (%)					
Randomized treatment	686 (54.0)	97 (48.7)	449 (45.5)	122 (48.6)	0.001
Digitalis	1141 (89.8)	186 (93.5)	933 (94.6)	239 (95.2)	<0.001
Diuretic	1156 (91.0)	190 (95.5)	946 (95.9)	241 (96.0)	<0.001

ACE inhibitor	1168 (91.9)	183 (92.0)	886 (89.9)	232 (92.4)	0.308
ACE inhibitor or ARB	1241 (97.6)	195 (98.0)	942 (95.5)	239 (95.2)	0.016
Spironolactone	35 (2.8)	4 (2.0)	43 (4.4)	10 (4.0)	0.121
ICD	36 (2.8)	4 (2.0)	46 (4.7)	4 (1.6)	0.020
Pacemaker	95 (7.5)	19 (9.5)	93 (9.4)	24 (9.6)	0.328
Laboratory measures					
Serum creatinine -mg/dl	1.16±0.36	1.26±0.43	1.32±0.44	1.31±0.40	<0.001
eGFR -ml/min/1.73m^2	74.2±23.8	69.4±23.8	65.8±25.5	64.4±22.1	<0.001
eGFR <60 ml/min/1.73m^2	347 (28.1)	70 (35.5)	427 (44.4)	118 (48.0)	<0.001

ACE denotes angiotensin converting enzyme; ARB, angiotensin II receptor antagonist; BMI, body mass index; CABG, coronary artery bypass grafting; CV, cardiovascular; ED, emergency department; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

*Heart failure duration is presented as median with interquartile range.

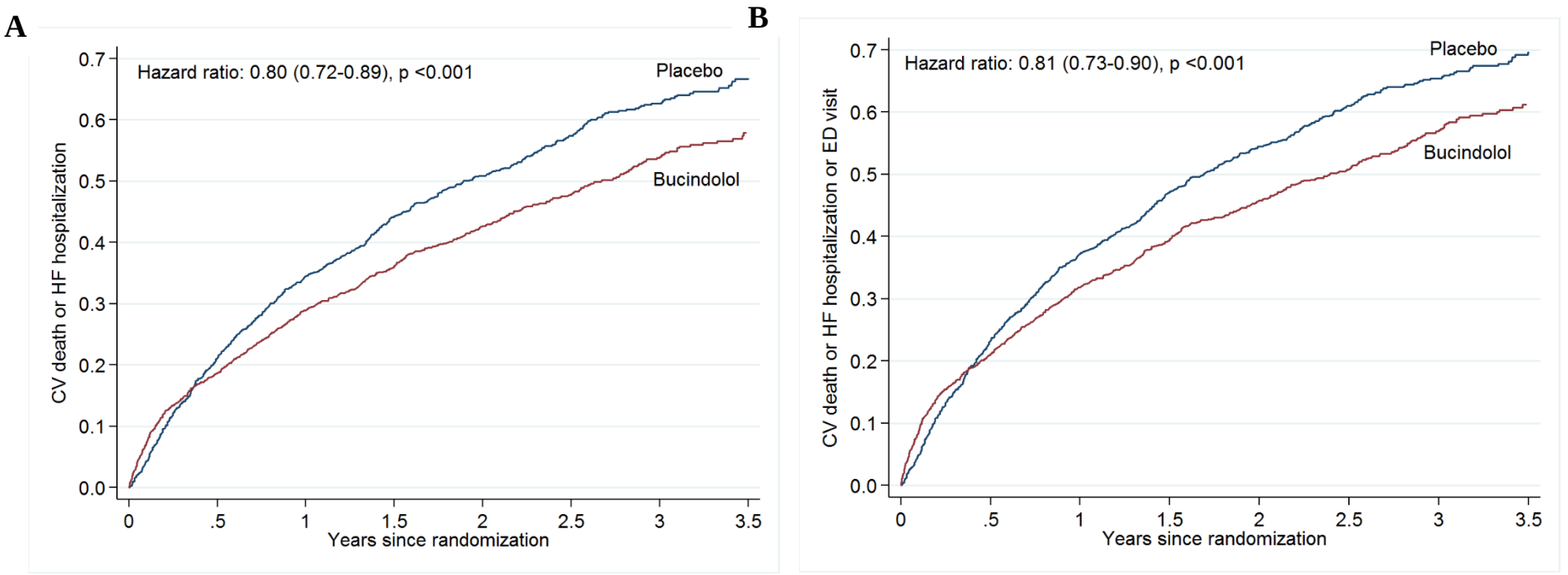
Table 3 Treatment effects (bucindolol versus placebo) on all heart failure hospitalizations (first and recurrent) and the composite of all heart failure hospitalizations and cardiovascular deaths using different methods to analyse recurrent events.

	Entire follow-up		within 6 months		beyond 6 months	
	HR/RR (95% CI)	**p value**	**HR/RR (95% CI)**	**p value**	**HR/RR (95% CI)**	**p value**
Time to 1st HF hospitalization	0.78 (0.69-0.89)	<0.001	0.88 (0.73-1.06)	0.190	0.72 (0.61-0.84)	<0.001
All HF hospitalizations						
LWYY	0.82 (0.71-0.95)	0.008	0.98 (0.80-1.21)	0.880	0.77 (0.65-0.91)	0.002
WLW	0.80 (0.68-0.94)	0.005	0.99 (0.80-1.23)	0.940	0.74 (0.62-0.89)	0.001
Negative binomial	0.89 (0.77-1.04)	0.137	1.00 (0.82-1.24)	0.970	0.80 (0.68-0.95)	0.010
Joint frailty*	0.89 (0.77-1.04)	0.128	1.02 (0.82-1.27)	0.840	0.80 (0.67-0.95)	0.010
All HF hospitalizations & CV death						
LWYY	0.83 (0.73-0.94)	0.003	0.97 (0.80-1.18)	0.770	0.78 (0.67-0.90)	0.001
WLW	0.80 (0.69-0.92)	0.002	0.98 (0.80-1.19)	0.840	0.75 (0.64-0.88)	<0.001
Negative binomial	0.89 (0.78-1.01)	0.066	1.00 (0.82-1.21)	0.990	0.80 (0.69-0.93)	<0.001

CI denotes confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LWYY, Lin, Wei, Ying and Yang model; RR, rate ratio; WLW, Wei, Lin and Weissfeld model.

*The corresponding HR for CV death in the joint frailty model was 0.93 (95% CI 0.77-1.13, p=0.47) in the entire follow-up, 1.02 (95% CI 0.72-1.44, p= 0.91) within 6 months, and 0.86 (95% CI 0.69-1.07, p=0.17) beyond 6 months.

Figure 1 Kaplan-Meier curves for composite outcome (A) and the expanded composite outcome (B) according to treatment group.



CV denotes cardiovascular; ED, emergency department; HF, heart failure.

Figure 2 Estimated cumulative rate of heart failure hospitalizations per 100 patients over time by treatment group and the corresponding risk ratio (bucindolol versus placebo) for the cumulative rate of heart failure hospitalizations.